The art of stacking: structural folding and self-assembly of branched π-conjugation assisted by O–H···O and C–H···F hydrogen bonds†‡

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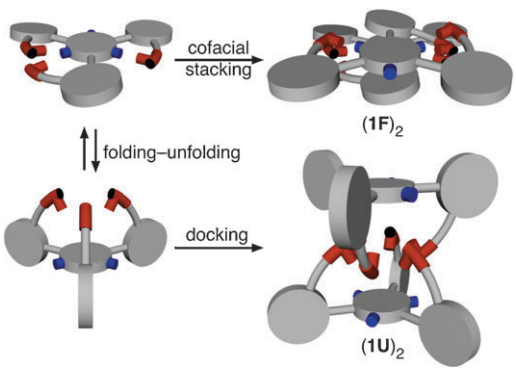
An intimate interplay of O–H···O/C–H···F hydrogen bonds and π–π stacking interactions allows a phenyleneethynylene-based dendritic molecule to fold and self-assemble into two distinctively different molecular crystals as pseudopolymorphs.

Polymorphism describes the ability of molecules to adopt more than one structure in the solid state.[1] When polymorphs occur with variations in solvent contents in the unit cell, the term *pseudo*polymorphism is used.[2] A practical importance of this phenomenon has been recognised in the field of pharmaceuticals since (pseudo)polymorphs often display different physicochemical properties.[1a,1c,3,4] In this communication, we report *pseudo*polymorphism of a phenyleneethynylene-based C_3-symmetric π-conjugated molecule. Structure analysis on two distinctively different molecular crystals revealed an intimate interplay of strong O–H···O and weak C–H···F hydrogen bonds in structural folding and solid-state self-assembly (Scheme 1), a detailed understanding of which was also aided by theoretical studies.

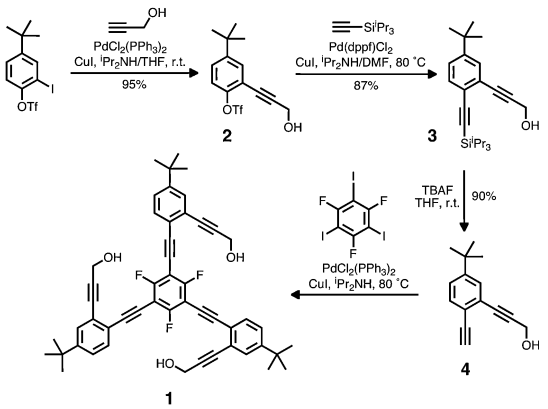
Hydrogen bonding is one prominent type of non-covalent interaction, the directional nature of which is proven to play a critical role in the spontaneous structural ordering of many chemical architectures.[5] While strong hydrogen bonds are typically constructed using N–H···O, O–H···O, or O–H···N motifs, weak hydrogen bonds involving C–H···O, C–H···N, or C–H···π contacts have recently been recognised as an important class of non-covalent interactions.[6] Recent examples of linear foldamers and heterodimers that are stabilised by N–H···F hydrogen bonding support the notion that organofluorine fragments can also be utilised as a hydrogen bonding acceptor (HBA) for the assembly of higher-order structures.[7] Undoubtedly, the charged F^- anion is a strong HBA,[8] but the ability of covalently bound fluorine atom, as present in the C–F group, to function as an effective HBA still remains controversial.[9–12] Statistical analysis on crystallographically determined structures suggests, however, that C–H···F interactions could be as important as C–H···O or C–H···N hydrogen bonds.[13]



Scheme 1 Conformational switching to achieve shape complementarity for self-association.

Our on-going interest in the conformational switching of branched π-conjugated structures[14] prompted the design and synthesis of a new phenyleneethynylene-based C_3-symmetric molecule **1** having a fluorinated molecular core (Scheme 2).‡ The final round of cross-coupling between **4** and 1,3,5-trifluoro-2,4,6-triiodobenzene resulted in a mixture of the desired product **1**, along with partially coupled byproducts and the homocoupling product of **4**. A simple layering of hexanes over a $CHCl_3$ solution of this material, however, induced selective crystallization of **1**, which was isolated and fully characterised (Fig. S1).‡

Self-association of **1** in solution was subsequently investigated by concentration-dependent ^1H NMR studies in $CDCl_3$ at T = 298 K. A systematic downfield shift of the propargylic O–H resonance from 2.52 to 2.73 ppm with increasing concentration within the range of 10 to 40 mM could be fitted with K = 4.1 (±0.5) M^{-1} using the EK model.[15] This observation implicated the involvement of O–H···O hydrogen bonding in the self-association process, which should become more favorable with decreasing polarity in the $CHCl_3$/hexane binary solvent mixture used in crystallization.



Scheme 2 Synthetic route to **1**.

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‡ Electronic supplementary information (ESI) available: Details of the synthetic procedures, crystallographic data, and DFT calculations. CCDC 783201 and 783202. For ESI and crystallographic data in CIF or other electronic format, see DOI: 10.1039/c0cc02177f

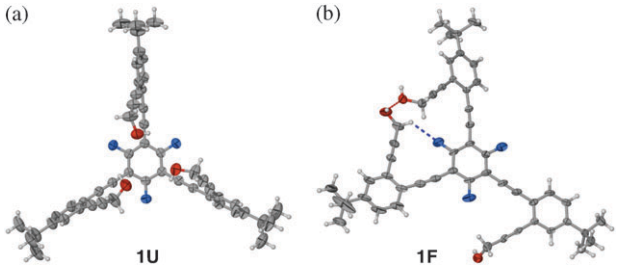


Fig. 1 X-Ray structures of **1U** (a) and **1F** (b) with thermal ellipsoids at 50% probability, where O is red and F is blue. The O–H···O and C–H···F interactions are represented by red and blue dotted lines, respectively.

Intriguingly, two different kinds of single crystals of **1** were obtained depending on the method of crystallization.§ Specifically, colorless blocks of the completely "unfolded" conformer **1U** (Fig. 1a) were obtained by slow diffusion of hexane into a $CHCl_3$ solution of **1**.[16] On the other hand, an instant mixing of a $CHCl_3$ solution of **1** with hexane or benzene produced colorless needles of the "folded" conformer **1F** (Fig. 1b),[16] which was also characterised by single crystal X-ray crystallography. As shown in Fig. 1 and S2 (ESI‡), the fluorinated benzene core and peripheral aryl groups in **1U** are disposed in an essentially perpendicular manner with dihedral angles of τ = 79.3(2) and 83.4(7)°.[17,18] For the other conformer **1F**, however, two of the three ethynyl-extended "wingtip" O–H groups engage in an intramolecular O–H···O hydrogen bond (O···O = 2.731(4) Å), which, along with C–H···F contact to the fluorinated core (C···F = 3.209(5) Å), effectively flattens the entire structure with relatively small τ values of 9.0(2), 14.1(2), and 35.5(1)°.[18]

A close inspection of the intermolecular packing in the lattice provided an initial clue to the origin of conformational isomerism of **1**. Instead of making *intramolecular* O–H···O bond as in **1F** (Fig. 1b), **1U** uses strong *intermolecular* O–H···O hydrogen bonds (O···O = 2.689(5) Å) to form a discrete dimeric structure $(\mathbf{1U})_2$. As shown in Fig. 2 and S3 (ESI‡), the two **1U** units comprising the dimer maximise their shape complementarity by adopting an essentially "staggered" orientation, in which two C_3-symmetric molecules are rotated

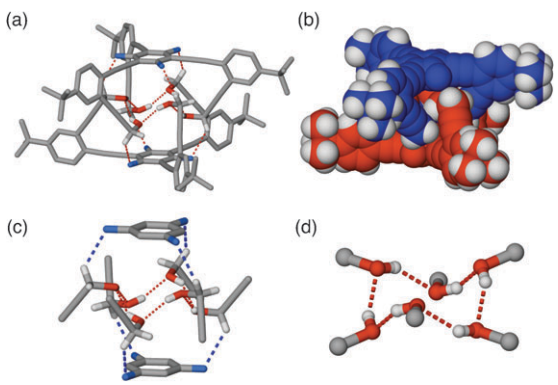
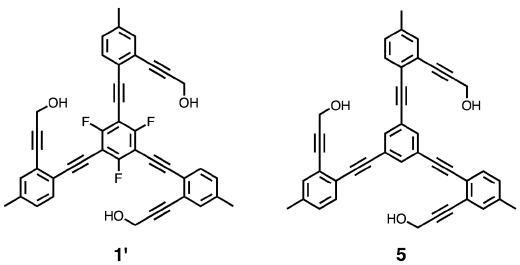


Fig. 2 Capped stick (a) and space-filling (b) representations of the solid-state structure of dimeric $(\mathbf{1U})_2$ generated using X-ray coordinates. The O–H···O and C–H···F interactions are represented by dotted lines, the close-up views of which are provided in partial structures (c) and (d).

by 60 degrees with respect to each other to achieve a tight docking.

An interdigitated arrangement of phenyleneethynylene fragments in the dimeric $(\mathbf{1U})_2$ thus provides a well-shielded hydrophobic cavity that encapsulates a cyclic hydrogen bonding network constructed by six "wing-tip" OH groups (Fig. 2c and d). A more fascinating feature of the dimeric $(\mathbf{1U})_2$ is additional stabilization provided by six C–H···F contacts between the propargyl C–H groups and the fluorinated benzene core (Fig. 2a and c). The relatively short C···F distance of 3.228(8) Å observed here lies toward the shorter end of the values determined for previously reported structures.[13a,13c–e,19–21]

The functional relevance of such C–H···F contacts in the self-assembly process was evaluated further by density functional theory (DFT) computational studies on the simplified model compounds **1′** and **5** (at B3LYP/6-31G** theory level). The *pseudo* D_{3d}-symmetric optimised geometry (Fig. S4, ESI‡) of $(\mathbf{1'})_2$ provided an average value of d(F···H) = 2.45 Å along the C–H···F contacts, which is *ca.* 0.17 Å shorter than the sum of van der Waals radii of F and H.



Energy evaluation at the B3LYP/cc-pVTZ(-f) level further supported the notion that such C–H···F interactions contribute to the thermodynamic stability of the dimer. Specifically, $(\mathbf{1'})_2$ is stabilised by 7.4 kcal mol^{-1} relative to the essentially isostructural $(\mathbf{5})_2$ lacking the C–F units (Fig. S5, ESI‡), when the energy difference between the individual monomers and the corresponding dimers was compared (Fig. S6, ESI‡). Divided by the total number of contacts within the dimer, each C–H···F interaction contributes to the overall stability by *ca.* 1.2 kcal mol^{-1}.

Similarly to the self-association of **1U**, its conformational isomer **1F** also forms a dimeric structure in the solid state, but the topology of $(\mathbf{1F})_2$ is determined by a quite different set of non-covalent interactions. As shown in Fig. 1b, **1F** adopts a planar conformation, which is anticipated to promote cofacial stacking. Indeed, the assembly of dimeric $(\mathbf{1F})_2$ is assisted by π–π stacking (*ca.* 3.38 Å) between electron-deficient fluorinated benzene core and electron-rich *tert*-butyl-substituted phenyl ring, the complementarity of which is further strengthened by the existence of two such contacts within the dimer (Fig. 3a–c).

In addition, the "dangling" OH group in the monomeric **1F** (Fig. 1b) engages in an intermolecular hydrogen bond (O···O = 2.654(4); 2.670(4) Å) to the O–H···O–H unit of the stacking partner (Fig. 3a and c) to complete an extended O–H···O–H···O–H array. Intriguingly, this crescent-shaped O–H···O–H···O–H motif on each side of $(\mathbf{1F})_2$ can further associate with the complementary O–H···O–H···O–H unit of the neighboring dimer to close up the six-membered cyclic

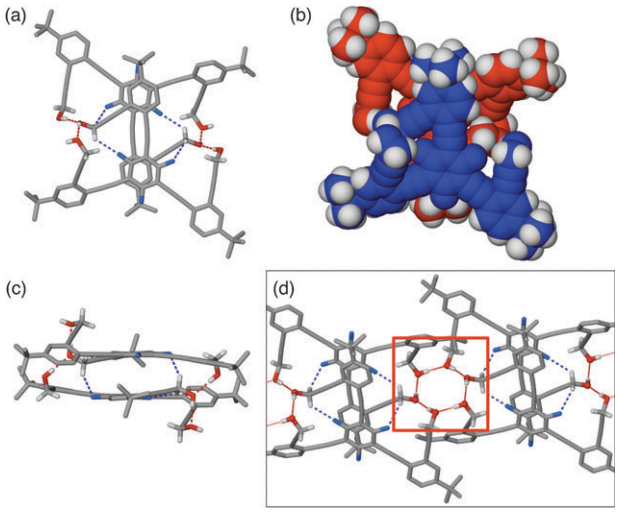


Fig. 3 Capped stick and space-filling representations of the solid-state structure of dimeric $(\mathbf{1F})_2$ generated using X-ray coordinates: (a) and (b) top view; (c) side view. In (d) is shown the extended structure of hydrogen-bonded $(\mathbf{1F})_2$ with hexameric OH cluster motif highlighted within a red box. The O–H···O and C–H···F interactions are represented by dotted lines.

hydrogen bond (Fig. 3d). The crystal structure of **1F** also revealed an intermolecular C–H···F contact (C···F = 3.207(5) Å).

In summary, an intimate interplay of O–H···O/C–H···F hydrogen bonds and π–π stacking collectively gives rise to conformational *pseudo*polymorphs of a dendritic π-conjugated molecule (Scheme 1). For the highly symmetric and non-planar conformer **1U**, a maximum number of O–H···O and C–H···F contacts is achieved by shape complementarity in monomer–monomer docking. For the less symmetric and largely planar conformer **1F**, the molecule takes a different strategy to maximise monomer–monomer contacts by using predominantly a combination of π–π stacking and O–H···O interactions. Efforts are currently underway in order to prepare chiral derivatives of the parent system and to explore further the functional role of C–H···F hydrogen bonds in supramolecular chemistry.

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Notes and references

§ Crystal data. **1U** (CCDC 783202) $C_{53.27}H_{47.27}Cl_{6.82}F_3O_3$ M = 1034.63, trigonal $R\bar{3}$, a = 17.1496(12) Å, c = 33.798(2) Å, V = 8608.5(9) Å^3, T = 150(2) K, Mo-Kα, 26 759 reflections, 3403 unique (R_{int} = 0.025). R_1 = 0.0905, wR_2 = 0.2683 (for 2596 observed reflections with $I > 2\sigma(I)$ and 276 parameters, 784 restraints). **1F** (CCDC 783201) $C_{51}H_{45}F_3O_3$ M = 762.87, triclinic $P\bar{1}$, a = 10.4830(8) Å, b = 14.9544(12) Å, c = 15.7398(13) Å, α = 89.095(2)°, β = 86.983(2)°, γ = 71.805(2)°, V = 2340.9(3) Å^3, T = 150(2) K, Mo-Kα, 29 791 reflections, 7914 unique (R_{int} = 0.045). R_1 = 0.0691, wR_2 = 0.2059 (for 5124 observed reflections with $I > 2\sigma(I)$ and 523 parameters, 12 restraints). The contribution of the diffuse contributing solvent (= two $CHCl_3$ per molecule of **1F**) to the structure factors was assessed by back-Fourier transformation, and the data were corrected accordingly using Platon/SQUEEZE. The sum formula of **1F** excludes these solvent molecules.

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9 Understanding the supramolecular chemistry of C–F group is thus considered as one of the last frontiers in intermolecular interactions[1e].

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16 In analogy to protein secondary structures, the term "folding" here describes conformational restrictions imposed by non-covalent bonds.

17 The structure of **1F** is disordered over two positions, for which only one model is shown in Fig. 1 and 2. See ESI‡.

18 The dihedral angle here is the angular relationship between the central C_6F_3 fragment and the peripheral aryl rings, all treated as least squares planes calculated from crystallographic data. In this analysis, τ = 90° corresponds to a perfectly orthogonal arrangement, whereas τ = 0° corresponds to a perfectly coplanar arrangement.

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